REMARKS

Claims 1 through 24 are pending in this patent application. New claim 25 has been added. Claims 1, 5, 6, 10, 11, 12, 18, 19, and 24 have been amended to more distinctively claim Applicant's invention. Claims 2, 3, 15, 16 and 20 have been cancelled.

Support for the amendments can be found, for example, as follows: for amended claim 1 in claims 1, 3, and 10 as filed, for amended claim 5 in claims 1 and 5 as filed, for amended claim 6 in claim 6 as filed, for amended claim 10 in claim 10 as filed, for amended claim 11 in claims 11, 16, and 10 as filed, for amended claim 12 in claim 12 as filed, for amended claim 18 in claims 18 and 11 as filed, for amended claim 19, in claims 19, 3, and 10 as filed, for amended claim 24, in claims 24, 3, and 10 as filed, for new claim 25, in claims 1, 3, 6, and 10 as filed.

Compliance with Sequence Rules

The specification was objected to because it failed to comply with the requirements of 37 C.F.R. §§1.821 through 1.825.

Paragraphs [0021] and [0064] of the specification have been amended so that all sequences are now identified by a SEQ ID NO.

Submitted at this time are:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing".

A statement under 37 C.F.R. §§1.821-1.825 that the content of the paper and computer readable copies are the same and include no new matter.

Applicants are requesting entry of the amended "Sequence Listing" presently submitted.

In addition to the amendment of paragraph [0064] requested by Examiner, Applicants have amended paragraph [0021], which describes FIG. 1. Depicted in FIG. 1 are SEQ ID NO: 1 and SEQ ID NO: 2. SEQ ID NO: 3 and SEQ ID NO: 1, which were both present in the original specification, differ in that SEQ ID NO: 3 has and additional T residue at position 6 of SEQ ID NO: 1. Applicants apologize for the confusion this discrepancy has caused. While a primer of SEQ ID NO: 3 was used in the amplification of Example 1, a primer of SEQ ID NO: 3 is an acceptable substitute for the same process.

Specification

Examiner has objected under 35 U.S.C. §132 to the amendment filed 4/7/03 because it introduced new matter into the disclosure.

Former SEQ ID NO: 3 is deleted in the accompanying "Sequence Listing". Current SEQ ID NO: 3, as explained above, was present in the original specification.

Claim rejections – 35 U.S.C. §112

New Matter

Claims 1-24 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

This rejection is avoided by amendment. Specifically, recitations of "a genetic vaccine utilizing a recombinant vector or modified polypeptides" and "antigens that do not cause a destructive form of acne" have been deleted. Consequently, withdrawal of this rejection is requested.

Scope of Enablement

Claims 1-24 stand rejected under 35 U.S.C. §112, first paragraph, because the specification fails to enable the full scope of the claimed invention.

Claims 2, 3, 15, 16, and 20 have been cancelled, and the remaining claims have been amended. Applicants submit that the current claim amendments make discussion of some of the points raised by the Examiner in the previous Office Action unnecessary. Specifically, Applicants believe it unnecessary to presently address Examiner's remarks regarding lack of enablement of complete prevention of conditions caused by *P. acnes*, and the significance of any reports of weak or undetectable humoral immune responses against the *P. acnes* phosphatase and hyaluronase. This is because the claims as amended do not require prevention, and recite only the *P. acnes* lipase as an antigen. The remaining concerns of the Examiner are addressed below.

Examiner relies on McCluskie to conclude that extrapolation of genetic immunization results in mice to those that might be obtained in humans is unpredictable. Applicants respectfully disagree with this interpretation of the significance of the McCluskie reference for the following reasons.

McCluskie addresses only naked DNA vaccines, not virus mediated immunization

The scope of McCluskie does not include viral based vaccines. Claims 5, 6, and 18 as amended specifically recite "adenovirus, adeno-associated virus, herpes virus, vaccinia and RNA viruses" or "an adenovirus". These claims as amended do not cover naked DNA, and therefore McCluskie cannot support their rejection for lack of enablement under 35 U.S.C. §112, first paragraph. Thus, the limited focus of McCluskie on DNA vaccines is a reason additional to those discussed below for allowance of claims 5, 6, and 18 as amended.

The results presented by McCluskie are of questionable scientific value due to serious flaws in the experimental design

Examiner uses the McCluskie study to support the conclusion that genetic vaccination results of mice do not predict similar results in primates, and likely in humans. Comparison of mice and primate responses to DNA vaccines, such as those reported in McCluskie, are of dubious relevance. Significant differences are to be expected because of the way mice are injected, not the immunology. In mice disproportionately large dosage and injection volumes are used. In the case of intramuscular injections, for example, mice muscles get blown up like balloons, basically

forcing DNA into the cells. Proportional injection volumes cannot be used in primates (50 µl into a mouse muscle would be equivalent to approximately 100 cc into a monkey muscle). Consequently, results obtained in mice and primates cannot be easily compared.

The flaw of the McCluskie study is quite obvious. In fact, it is essentially acknowledged in the reference itself. On page 296, second full paragraph, McCluskie states that "[t]he relatively greater efficacy of IM in mice than primates may be related to morphological differences. Alternatively, it may be more related to dosage. The 10- to 100- µg doses of DNA vaccine typically used in a 20-g mouse would be equivalent to 35 to 350 mg in a 70-kg human, a dose range greatly in excess of what has been used to date in human clinical trials". Thus, the results of the McCluskie study cannot substantiate the view that mice immune response to DNA vaccines do not predict similar results in humans.

Others did not share the opinions expressed in McCluskie

Apparently aside from the results presented in McCluskie, Examiner quotes certain language from the McCluskie reference to support the view that results of DNA vaccines in animals were not expected by those of skill in the art to be reproducible in humans. While such language may be useful to justify the McCluskie study, others did not share the view at the time. For example, McCluskie concludes that "[...] although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological response to the antigen". The Declaration of

Dr. Kumar filed 4/7/03 notes that there have been at least 509 gene therapy trials since the 1980's. This large number proves that those of skill in the art do not consider transfection and expression of vectors in human cells unpredictable by pre-clinical studies.

The fact that those of skill in the art considered DNA vaccine results in animals to be predictive of a similar response in humans is demonstrated by the implicit expectation of those workers in the DNA vaccine field seeking to develop treatments for human conditions. For example, Gerdts et al. (Nature Medicine, 6:929-932, 2000) developed fetal lamb immunization with a DNA vaccine as a relevant approach to treatment of neonatal morbidity and mortality in humans (page 929, first paragraph, left column). Also, Tacket et al. (Vaccine 17:2826-2829, 1999) reports human clinical trial results to a DNA vaccine. In pre-clinical studies the vaccine was used on mice (page 2827, left column, first full paragraph). Consequently, those of skill in the art did not share McCluskie's skeptical view of the significance of animal DNA vaccination results.

Applicants do not understand Examiner's position to be that animal research results are generally not predictive of similar human responses. Indeed, such a position would be untenable in view of judicial precedent and the common knowledge and practice in the pharmaceutical industry. Rather, Examiner concludes, based on McCluskie, that animal models are not useful only for DNA vaccines. As explained above, those of skill in the art do not regard McCluskie as authoritative. Therefore, Examiner's statements, such as "those of skill in the art still consider the extrapolation of genetic immunization results from mice to humans to be unjustified in view of the totality of the art" (pages 25-26 of the Office Action) are incorrect because such a view is based

only on a few sentences in the McCluskie reference, which are not representative of the totality of the art.

The specification contains sufficient details regarding administration of the vaccine to enable those skilled in the art to practice the invention

Examiner concludes, again based only on McCluskie, that immune responses to genetic vaccines are unpredictably dependent on the route of administration. Applicants respectfully submit that the examiner is incorrect. Despite some apparent dependency on the route of administration, the McCluskie reference reports that notable immune responses are elicited in most cases. Still, McCluskie is not a pioneering study, and various routes of administration were successfully used for DNA vaccination by others, as cited in McCluskie itself (see the paragraph bridging pages 288 and 289), or summarized in Lewis and Babiuk (Advances in Virus Research, 54:129-188, 1999). The McCluskie study is limited, for example, because the authors did not attempt to determine even the effect of well-known variables, such as adjuvants, on the immune responses. The specification provides significant directions regarding routes of administration at paragraphs [0041] to [0057]. Numerous examples of successful genetic immunization reports could be found in the art, and those of skill in the art could routinely optimize variables to successfully develop immunity. Examiner concludes on page 27, first full paragraph, that "[i]n view of the unpredictability of the art in general, as established above, one of skill in the art would have no reason to expect to obtain successful treatment of acne using these routes of administration". Applicants respectfully submit that this conclusion is in error because the totality of the art indicates

that DNA immunization was successful in a large number of cases, the application provides significant guidance regarding routes of administration and proves successful immunization with the claimed vaccines, and optimization of variables such as routes of administration was well within the potential of those of skill in the art without undue experimentation.

Example 2 demonstrates that the vaccine can treat *P. acnes*-related conditions

Examiner states in the Office Action that the specification is not enabling because the mouse is not an accepted model of acne vulgaris. Examiner cites De Young and Whyte in the paragraph bridging pages 12 and 13 regarding the use of rats and pigs as animal models for acne vulgaris. Applicants respectfully submit that Examiner attaches unwarranted weight to the fact that the mouse may not be an accepted model of acne vulgaris and the differences between rodent and human skin.

Implicit in Examiner's reasoning is that because the mouse is not an accepted model of acne vulgaris, the results of Example 2 are irrelevant to the treatment of acne vulgaris. Applicants vehemently disagree with such a position. Example 2 demonstrates that a robust and effective immune response to *P. acnes* is mounted in mice in response to a lipase expressing vaccine. As discussed above, and given the long practiced use of mice in immunology studies, a similar result would be expected in humans. Therefore, Example 2 shows that the disclosed vaccines elicit an immune response effective against *P. acnes*.

There is ample evidence to demonstrate that an immune response to the *P. acnes* lipase that effectively controls *P. acnes* is effective in treating *P. acnes*-caused

conditions. For one thing, as Examiner acknowledged on page 10, under "State of the prior art", "[t]he prior art taught the use of acne compositions comprising *P. acnes* bacteria and P acnes bacterial derivatives as acne vaccines". Thus, there is some expectation in the art that a vaccine-elicited immune response would help control acne.

Then, as explained in Dr. Kumar's 4/7/03 declaration on page 6, lines 9-15, the lipase is an excellent target for immunization because neutralizing antibodies are likely to inhibit bacterial cell growth, and because the lipase is secreted it will be displayed as a presented antigen, thus generating an effective cell-mediated response. Examiner replies at page 17 of the Office Action that the cited references "provide no evidence that inhibitory antibodies against these enzymes have been, or can be, produced". Applicants respectfully wish to direct Examiner's attention to Table 4 on page 810 of Ingham et al. (British Journal of Dermatology, 116:805-812, 1987), which shows that antibodies that inhibit the lipase enzymatic activity are produced in humans. Of course, Example 2 also leaves no doubt that immunization with the disclosed vaccine effectively controls a *P. acnes* challenge. Consequently, the accumulated knowledge in the art shows that immunity directed to the *P. acnes* lipase is effective.

An implication of Examiner's view is that even in the case of inflammatory acne, an anti-lipase immune response effective in controlling *P. acnes* would be useless as a treatment. As stated in the following section, current data does not indicate that an anti-lipase immune response contributes to any aspect of acne progression. Yet *P. acnes* is very likely to be a stimulus for acne inflammation (Webster, Int J Dermatol, 29:313-317, 1990; Badawy et al, Eur J Dermatol 2:8-11, 1992). It follows that an effective control of *P. acnes* by the immune system would remove at least some of the inflammatory

stimulus, thus alleviating the symptoms of inflammatory acne. Consequently, applicants submit that Example 2 and the general knowledge in the art regarding *P. acnes*- caused conditions demonstrate that the claimed vaccines are effective as a treatment.

Additionally, it is worth noting that rodents have actually been previously used in studying *P. acnes*- caused conditions (De Young et al., J Investigative Dermatology, 83:394-398, 1984; Brook, Journal of Medical Microbiology, 34:249-252, 1991). Examiner states at pages 12-13 that Whyte noted some limitations of the of the De Young rat model of acne and the comparative superiority of the pig model. Still, while the pig model may be superior to rodent models in some respects, it has its own limitations, and Whyte does not maintain that experiments performed on rodent models are irrelevant to human *P. acnes*- caused conditions.

Genetic vaccines can alleviate pre-existing conditions

The relevant text from the Office Action, page 14, is reproduced below in the indented text, followed by Applicants' response.

> **Regarding the treatment of existing conditions by genetic immunization, Irvine et al. (J. Immunol. 456:238-248, 1996) teach that "DNA immunization alone had little or no impact on the growth of established lung metastases", and Lewis et al. (Adv. Vir. Res. 54:128-188, 1999) note a case in which genetic immunization resulted in exacerbation of disease progression (see page 169, column 2, lines 1-3 of second paragraph). Furthermore, as noted in the specification and specific to the claimed invention, Karvonen et al. (Dermatology 189:344-349, 1994) and Holland et al. (Exp. Dermatol. 2:12-16, 1993) teach that immune responses to some P. acnes antigens can actually contribute to the disease process, although neither of these publications, nor Applicant's specification, identifies any of these antigens.**

The Irvine and Lewis instances noted by Examiner seem to be exceptional. Irvine was actually able succeed in treating existing conditions with the use of an adjuvant. Lewis does indeed note a case where immunization with naked DNA seems to exacerbate

disease progression, but Table V (pages 170-171) in Lewis presents numerous examples of successful genetic immunizations. The study noted by Lewis is highly unlikely to be relevant to the claimed invention. An explanation of the result suggested by the authors of that reference was that DNA immunization facilitated activation of B and T cells, thus augmenting replication of the subsequently administered feline immunodeficiency virus. Since unlike the feline immunodeficiency virus, *P. acnes* does not replicate inside B and T cells, that report appears to be unrelated to the instant application.

Karvonen performed crude tests to compare the levels of delayed hypersensitivity reaction, a type of cell-mediated immune response, to total *P. acnes* antigens from whole cells or cell extracts in patients with severe acne and normal controls. In doing so they were not able to determine which antigens contributed to the harmful response and which antigens did not. Also, the hypersensitivity reaction was not well characterized and could very well be an epiphenomenon, unrelated to *P. acnes*. Thus, they provide no evidence to prove that the *P. acnes* lipase induces hypersensitivity. Also, the results presented in Holland are not relevant to the claims as amended because the claims are limited to the *P. acnes* lipase. The significance the eight polypeptides of the Holland reference to acne etiology, if any, cannot be relevant to the claims as amended because the lipase was not one of the eight polypeptides ("[t]hese polypeptides were not related to described extracellular enzymes of *P. acnes*" page12, abstract). Thus, neither Karvonen nor Holland show that immune responses to the *P. acnes* lipase are harmful.

Written Description

Claims 1-24 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 2, 3, 15, 16, and 20 have been cancelled. The remaining claims have been amended to recite "a lipase or fragment thereof" instead of "at least one antigen". Applicants respectfully submit that the claims as amended are supported by an adequate written description. The sequence of the *P. acnes* lipase gene was known at the time the application was filed (Miskin J.E. *et al.* Microbiology, 143:1745-1755, 1997). Therefore, those of skill in the art could readily learn the *P. acnes* lipase sequence from the available literature or sequence databases. The specification teaches a method of obtaining the *P. acnes* lipase, and shows reduction to practice of the full-length gene (see Example 1). The lipase obtained by Applicants was identical at the amino acid level to the representative lipase reported by Miskin, as expected since *P. acnes* in known to produce only one type of exocellular lipase. Also, it is appreciated by those of skill in the art that a fragment of a polypeptide elicits an immune response cross-reactive with that of the full-length polypeptide. This case is indeed very different from cases such as *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016 (Fed. Cir. 1991), where essential claim elements were directed to genes whose sequence was unknown at the time of patent application filing.

Accordingly, Applicants respectfully submit that claims 1, 4-14, 17-19, and 21-24, as amended, satisfy the "written description" requirements of 35 U.S.C. 112, first paragraph and respectfully request the withdrawal of the rejection of the claims.

Claim Rejections – 35 USC §102

Claims 1-3, 7, 10-12, 15, 16, 20-22, and 24 stand rejected under 35 USC §102(b) as being anticipated by Stickl (US Patent 4,057,627, 11/8/1977), as evidenced by Taverne et al (Infection and Immunity 37(3):927-934 (9/1982).

Applicants respectfully traverse the rejection because Stickl does not disclose each and every element of the invention as claimed in claims 1, 7, 10-12, 21, 22, and 24. Claims 2, 3, 15, 16, and 20 have been cancelled.

Stickl discloses compositions comprising attenuated *P. acnes* and their use as oral vaccines for acne vulgaris. Examiner states that "[t]he Stickl disclosure anticipates the instant claims because inactivated *P. acnes* is considered to be a vector comprising nucleic acids encoding all *P. acnes* antigens" (page 28), and that "[a]n argument that the genetic vaccine of Stickl does not comprise a recombinant vector would be unpersuasive because the claims do not require that the vaccine must be recombinant" (page 29).

The invention as claimed in claims 1, 7, 10-12, 21, 22, and 24 is directed to compositions comprising "... at least one vector ...". Paragraph [0025] of the specification defines vector as "... a genetically engineered nucleic acid construct ...". The composition disclosed by Stickl does not comprise genetically engineered nucleic acid constructs. The nucleic acids present in the Stickl composition are essentially bacterial transcripts, bacterial chromosomes, possibly endogenous bacterial plasmids, and perhaps fragments thereof. Since these nucleic acids were not genetically engineered, they cannot be considered "vectors" as applicants defined the term. Generally, an

applicant may be his lexicographer as long as the meaning assigned to the term is not repugnant to the term's well-known usage (*see* MPEP 2111.01). Usage of the term "vector" as genetically engineered nucleic acid constructs, but not endogenous bacterial transcripts, chromosomes, or plasmids, is not repugnant to the term's well-known usage. Therefore, Stickl does not disclose the invention as claimed in claims 1, 7, 10-12, 21, 22, and 24.

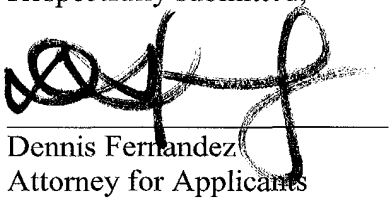
Accordingly, Applicants submit that the invention claimed in claims 1, 7, 10-12, 21, 22, and 24 is not anticipated by Stickl under 35 USC §102(b) and respectfully request the withdrawal of the rejection of the claims.

Applicants wish to thank Examiner for the courtesy of the telephone interview of August 26, 2003.

CONCLUSION

Claims 1, 2, and 4-37 are pending in this application. In view of the above, it is respectfully submitted by Applicants that the claims are in condition for allowance. Reconsideration of the rejections is requested. If the Examiner's action is other than allowance, the Examiner is requested to telephone Applicants' attorney at the number noted below.

Respectfully submitted,



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